## REMARKS

### I. Amendment to the Specification

The specification has been updated with respect to the cross referencing of related applications. In addition, a minor and inadvertent spelling error has been corrected in the paragraph bridging pages 10 and 11 of the specification. A clean version of the paragraphs upon entry of the preliminary amendment is provided in Appendix B. Thus, no new matter has been added to the specification.

### II. Amendments to the Claims

Claims 1-19, 22 and 23 have been canceled without prejudice. Claims 20 and 21 have been amended. Claims 24-59 have been added. Upon entry of the preliminary amendment, the claims will encompass, among other things, specific propellant-based compositions of a biologically active N-terminal fragment of parathyroid hormone. A clean version of the claims upon entry of the preliminary amendment is provided in Appendix B.

Support for the changes to the claims as well as the new claims is identified below. Additional support other than that identified below may exist in the specification for one or more changes and/or new claims.

Claim 20. Support for including a pharmaceutical bulking agent in the composition is provided in claim 5 as originally filed as well as on page 11, lines 8-11, and the sentence bridging pages 9 and 10 of the specification. Support for housing the composition "within a device designed for delivering an aerosolized bolus through the mouth" is provided in the abstract, on page 5, lines 7-9, and on page 12, lines 28-35. In combination, these passages support housing the claimed composition in a device (such as a nozzle or MDI) designed or intended primarily to deliver an aerosolized bolus through the mouth. The claimed composition is housed in the device prior to administration. In the case of an MDI, for example, the composition is usually housed in the canister portion of the device.

Claim 21. The changes made to claim 21 merely address matters related to form.

Claim 24. Aerosol propellants comprising a chlorofluorocarbon are supported by the sentence bridging pages 10 and 11 of the specification.

Claim 25. Specific chlorofluorocarbons are provided on page 11, lines 2-5, of the specification.

Claim 26. The specification discloses aerosol propellants comprising a hydrofluorocarbon in the sentence bridging pages 10 and 11.

Claim 27. Specific hydrofluorocarbons are recited on page 11, lines 5-7, of the specification.

Claim 28. Support for the subject matter of claim 28 is provided on page 5, lines 22-25, of the specification.

Claim 29. The bulking agents specifically provided in claim 29 are supported on page 10, lines 3-6, of the specification.

Claim 30. Support for PTH34 as an example of a biologically active N-terminal fragment of parathyroid hormone is found on page 8, lines 15-22, of the specification.

Claim 31. The specification discloses PTH38 as an example biologically active N-terminal fragment on page 8, lines 15-22.

Claim 32. General support for new independent claim 32 is found in claim 20 as originally filed. Support for compositions lacking a penetration enhancer is located on page 2, lines 25-27, of the specification. As in claim 20, support for housing the composition "within a device designed for delivering an aerosolized bolus through the mouth" is provided in the abstract, on page 5, lines 7-9, and on page 12, lines 28-35, of the specification.

Claim 33. Support for the subject matter of claim 33 is found in claim 21 as originally filed.

Claims 34, 35, 36, 37 and 38. See the comments with respect to claims 24, 25, 26, 27 and 28 for support of the subject matter of claims 34, 35, 36, 37 and 38, respectively.

Claim 39. Support for compositions comprising a bulking agent is found in the sentence bridging pages 9 and 10, and at page 11, lines 9-12, of the specification.

Claim 40. See the comments of claim 29 for support of the subject matter of claim 40.

Claim 41. Support for compositions further comprising an additive is found in specification in the paragraph bridging pages 9 and 10 (particularly at page 10, line 13) and at page 11, lines 8-19 (particularly at page 11, line 18).

Claim 42. Support for additives selected from the group consisting of surfactants, lower alcohols, chemical stabilizers and combinations thereof is found on page 11, lines 8-19, of the specification.

Claim 43. Specific support for surfactant additives is found on page 11, lines 11-13, of the specification.

Claim 44. The subject matter of claim 44 is found on page 11, lines 13-15, of the specification.

Claim 45. The subject matter of claim 45 is found on page 11, lines 8-13, of the specification.

Claim 46. Specific support in the specification for lower alcohol additives is found at page 11, lines 16-19.

Claim 47. Ethanol as an example of a lower alcohol is provided on page 11, lines 16-19, of the specification.

Claim 48. Specific support for chemical stability additives is found at page 11, lines 16-19, of the specification.

Claim 49. Support for the subject matter of claim 49 is found on page 10, lines 7-9, and on page 11, lines 8-11, of the specification.

Claim 50. Support for reciting a buffer as an example of a chemical stabilizer is provided on page 10, lines 7-9, and on page 11, lines 8-11, of the specification.

Claim 51. The subject matter of claim 51 is found on page 10, lines 9-11, of the specification.

Claim 52. A salt as an example of a chemical stabilizer is provided on page 10, lines 7-9, and on page 11, lines 8-11, of the specification.

Claim 53. The specific examples of salts recited in claim 53 are supported on page 10, lines 11-13, of the specification.

Claims 54 and 55. See the comments with respect to claims 30 and 31 for support of the subject matter of claims 54 and 55, respectively.

Claim 56. A method for treating a mammalian host suffering from or at risk of osteoporosis is provided on page 4, lines 12-17, of the specification. Support for "administering by inhalation through the mouth" and "an aerosolized bolus" is found on page 5, lines 7-9, of the specification. A therapeutically effective amount of a biologically active N-terminal fragment of

parathyroid hormone is located on page 12, lines 28-35, in the specification. See the comments provided above with respect to claim 20 for support of the pharmaceutical composition recited in claim 56.

Claim 57. Support for humans as an example of a mammalian host is provided on page 4, lines 12-17, of the specification.

Claim 58. With the exception of the recited composition, see the comments provided above with respect to claim 56 for support of the subject matter of claim 58. Support for the pharmaceutical composition discussed in claim 58 is provided above with respect to claim 32.

Claim 59. Support for humans as an example of a mammalian host is provided on page 4, lines 12-17, of the specification.

As support for the claimed subject matter is found in the application as filed, no new matter is introduced by the entry of the above-identified changes to the claims.

**III. Conclusion**

In view of the foregoing, Applicant submits that the pending claims satisfy the requirements of patentability and are therefore in condition for allowance. Consequently, a prompt mailing of a Notice of Allowance is earnestly solicited.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 620-5506.

Respectfully submitted,
Inhale Therapeutic Systems, Inc.

Date: August 28, 2002

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**Appendix A**
**Marked Version Showing Changes Made**

Entry and consideration of the following changes are respectfully requested. Additions are underlined and deletions appear with a strikethrough.

**In the Specification:**

Please delete the paragraph appearing on page 1, beginning at line 5, and substitute therefor the following paragraph:

**CROSS REFERENCE TO RELATED APPLICATIONS**

This application is a continuation of, and claims the benefit of priority from, application Ser. No. 09/128,401; filed on Aug. 3, 1998, now U.S. Pat. No. 6,080,721, which is a division of application Ser. No. 08/625,586; filed on Mar. 28, 1996, now U.S. Pat. No. 5,814,607, which is a continuation of application Ser. No. 08/232,849; filed on Apr. 25, 1994, now U.S. Pat. No. 5,607,915, which is a continuation of application Ser. No. 07/953,397; filed on Sep. 29, 1992, now abandoned, the full disclosures of which are incorporated herein by reference.

Please delete the paragraph bridging pages 10 and 11, and substitute therefor the following paragraph:

For use in MDI's, the PTH fragments of the present invention will be dissolved or suspended in a suitable aerosol propellant, such as a chlorofluorocarbon (CFC) or a hydrofluorocarbon (HFC). Suitable CFC's include trichloromonofluoromethane (propellant 11), ~~dichlorotetrafluoromethane~~ dichlorotetrafluoroethane (propellant 114), and dichlorodifluoromethane (propellant 12). Suitable HFC's include tetrafluoroethane (HFC-134a) and heptafluoropropane (HFC-227).

**In the Claims:**

Please cancel claims 1-19, 22 and 23 without prejudice. Please amend claims 20 and 21 and add new claims 24-59 as follows:

20. (Amended) A pharmaceutical composition ~~comprising~~ consisting essentially of a biologically active N-terminal fragment of parathyroid hormone ~~(PTH)~~, a pharmaceutically acceptable bulking agent and an aerosol propellant, wherein the composition is housed within a device designed for delivering an aerosolized bolus through the mouth ~~present as a powder having a mean particle size in the range from 0.5 μm to 5 μm present in an aerosol propellant~~.

21. (Amended) ~~A~~ The pharmaceutical composition ~~as in~~ of claim 20, wherein the aerosol propellant ~~is~~ comprises a chlorofluorocarbon or a hydrofluorocarbon.

24. (New) The pharmaceutical composition of claim 20, wherein the aerosol propellant comprises a chlorofluorocarbon.

25. (New) The pharmaceutical composition of claim 24, wherein the chlorofluorocarbon is selected from the group consisting of trichloromonofluoromethane, dichlorotetrafluoroethane, dichlorodifluoromethane, and combinations thereof.

26. (New) The pharmaceutical composition of claim 20, wherein the aerosol propellant comprises a hydrofluorocarbon.

27. (New) The pharmaceutical composition of claim 26, wherein the hydrofluorocarbon is selected from the group consisting of tetrafluoroethane, heptafluoropropane, and combinations thereof.

28. (New) The pharmaceutical composition of claim 20, wherein the composition comprises a powder having a mean particle size in the range from 0.5 μm to 5 μm.

29. (New) The pharmaceutical composition of claim 20, wherein the bulking agent is selected from the group consisting of sucrose, lactose, trehalose, human serum albumin, glycine,

cellobiose, dextrans, maltotriose, pectin, sodium citrate, sodium ascorbate, mannitol, and combinations thereof.

30. (New) The pharmaceutical composition of claim 20, wherein the biologically active N-terminal fragment of parathyroid hormone is PTH34.

31. (New) The pharmaceutical composition of claim 20, wherein the biologically active N-terminal fragment of parathyroid hormone is PTH38.

32. (New) A pharmaceutical composition comprising a biologically active N-terminal fragment of parathyroid hormone and a propellant, wherein the composition lacks a penetration enhancer and further wherein the composition is housed within a device designed for delivering an aerosolized bolus through the mouth.

33. (New) The pharmaceutical composition of claim 32, wherein the aerosol propellant comprises a chlorofluorocarbon or a hydrofluorocarbon.

34. (New) The pharmaceutical composition of claim 32, wherein the aerosol propellant comprises a chlorofluorocarbon.

35. (New) The pharmaceutical composition of claim 34, wherein the aerosol propellant is selected from the group consisting of trichloromonofluoromethane, dichlorotetrafluoroethane, dichlorodifluoromethane, and combinations thereof.

36. (New) The pharmaceutical composition of claim 32, wherein the aerosol propellant is a hydrofluorocarbon.

37. (New) The pharmaceutical composition of claim 36, wherein the aerosol propellant is selected from the group consisting of tetrafluoroethane, heptafluoropropane, and combinations thereof.

38. (New) The pharmaceutical composition of claim 32, wherein the composition comprises a powder having a mean particle size in the range from 0.5 μm to 5 μm.

39. (New) The pharmaceutical composition of claim 32, further comprising a bulking agent.

40. (New) The pharmaceutical composition of claim 39, wherein the bulking agent is selected from the group consisting of sucrose, lactose, trehalose, human serum albumin, glycine, cellobiose, dextrans, maltotriose, pectin, sodium citrate, sodium ascorbate, mannitol, and combinations thereof.

41. (New) The pharmaceutical composition of claim 32, wherein the composition further comprises an additive.

42. (New) The pharmaceutical composition of claim 41, wherein the additive is selected from the group consisting of surfactants, lower alcohols, chemical stabilizers and combinations thereof.

43. (New) The pharmaceutical composition of claim 42, wherein the additive is a surfactant.

44. (New) The pharmaceutical composition of claim 43, wherein the surfactant is selected from the group consisting of oleic acid, sorbitan trioleate, long chain diglycerides, phospholipids, and combinations thereof.

45. (New) The pharmaceutical composition of claim 43, wherein the composition comprises a powder comprised of particles and further wherein the particles are coated with the surfactant.

46. (New) The pharmaceutical composition of claim 41, wherein the additive is a lower alcohol.

47. (New) The pharmaceutical composition of claim 46, wherein the lower alcohol is ethanol.

48. (New) The pharmaceutical composition of claim 41, wherein the additive is a chemical stabilizer.

49. (New) The pharmaceutical composition of claim 48, wherein the chemical stabilizer is selected from the group consisting of buffers, salts, and combinations thereof.

50. (New) The pharmaceutical composition of claim 49, wherein the chemical stabilizer is a buffer.

51. (New) The pharmaceutical composition of claim 50, wherein the buffer is selected from the group consisting of phosphate buffers, citrate buffers, acetate buffers, tris-HCl buffers, and combinations thereof.

52. (New) The pharmaceutical composition of claim 45, wherein the wherein the chemical stabilizer is a salt.

53. (New) The pharmaceutical composition of claim 52, wherein the salt is selected from the group consisting of sodium chloride, sodium carbonate, calcium chloride, and combinations thereof.

54. (New) The pharmaceutical composition of claim 32, wherein the biologically active N-terminal fragment of parathyroid hormone is PTH34.

55. (New) The pharmaceutical composition of claim 32, wherein the biologically active N-terminal fragment of parathyroid hormone is PTH38.

56. (New) A method for treating a mammalian host suffering from or at risk of osteoporosis comprising administering by inhalation through the mouth of the host an aerosolized bolus of a pharmaceutical composition consisting essentially of a therapeutically effective amount of a biologically active N-terminal fragment of parathyroid hormone, a pharmaceutically acceptable bulking agent and an aerosol propellant.

57. (New) The method of claim 56, wherein the mammalian host is human.

58. (New) A method for treating a mammalian host suffering from or at risk of osteoporosis comprising administering by inhalation through the mouth of the host an aerosolized bolus of a pharmaceutical composition comprised of a therapeutically effective amount of a biologically active N-terminal fragment of parathyroid hormone and a propellant, wherein the composition lacks a penetration enhancer.

59. (New) The method of claim 58, wherein the mammalian host is human.

**Appendix B**
**Clean Version Upon Entry of the Preliminary Amendment**

**In the Specification:**

On page 1, beginning at line 5, the substituted paragraph will read:

## CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of, and claims the benefit of priority from, application Ser. No. 09/128,401; filed on Aug. 3, 1998, now U.S. Pat. No. 6,080,721, which is a division of application Ser. No. 08/625,586; filed on Mar. 28, 1996, now U.S. Pat. No. 5,814,607, which is a continuation of application Ser. No. 08/232,849; filed on Apr. 25, 1994, now U.S. Pat. No. 5,607,915, which is a continuation of application Ser. No. 07/953,397; filed on Sep. 29, 1992, now abandoned, the full disclosures of which are incorporated herein by reference.

The substituted paragraph bridging paragraphs 10 and 11 will read:

For use in MDI's, the PTH fragments of the present invention will be dissolved or suspended in a suitable aerosol propellant, such as a chlorofluorocarbon (CFC) or a hydrofluorocarbon (HFC). Suitable CFC's include trichloromonofluoromethane (propellant 11), dichlorotetrafluoroethane (propellant 114), and dichlorodifluoromethane (propellant 12). Suitable HFC's include tetrafluoroethane (HFC-134a) and heptafluoropropane (HFC-227).

**In the Claims**:

The claims will read:

20. A pharmaceutical composition consisting essentially of a biologically active N-terminal fragment of parathyroid hormone, a pharmaceutically acceptable bulking agent and an aerosol propellant, wherein the composition is housed within a device designed for delivering an aerosolized bolus through the mouth.

21. The pharmaceutical composition of claim 20, wherein the aerosol propellant comprises a chlorofluorocarbon or a hydrofluorocarbon.

24. The pharmaceutical composition of claim 20, wherein the aerosol propellant comprises a chlorofluorocarbon.

25. The pharmaceutical composition of claim 24, wherein the chlorofluorocarbon is selected from the group consisting of trichloromonofluoromethane, dichlorotetrafluoroethane, dichlorodifluoromethane, and combinations thereof.

26. The pharmaceutical composition of claim 20, wherein the aerosol propellant comprises a hydrofluorocarbon.

27. The pharmaceutical composition of claim 26, wherein the hydrofluorocarbon is selected from the group consisting of tetrafluoroethane, heptafluoropropane, and combinations thereof.

28. The pharmaceutical composition of claim 20, wherein the composition comprises a powder having a mean particle size in the range from 0.5 μm to 5 μm.

29. The pharmaceutical composition of claim 20, wherein the bulking agent is selected from the group consisting of sucrose, lactose, trehalose, human serum albumin, glycine, cellobiose, dextrans, maltotriose, pectin, sodium citrate, sodium ascorbate, mannitol, and combinations thereof.

30. The pharmaceutical composition of claim 20, wherein the biologically active N-terminal fragment of parathyroid hormone is PTH34.

31. The pharmaceutical composition of claim 20, wherein the biologically active N-terminal fragment of parathyroid hormone is PTH38.

32. A pharmaceutical composition comprising a biologically active N-terminal fragment of parathyroid hormone and a propellant, wherein the composition lacks a penetration enhancer

and further wherein the composition is housed within a device designed for delivering an aerosolized bolus through the mouth.

33. The pharmaceutical composition of claim 32, wherein the aerosol propellant comprises a chlorofluorocarbon or a hydrofluorocarbon.

34. The pharmaceutical composition of claim 32, wherein the aerosol propellant comprises a chlorofluorocarbon.

35. The pharmaceutical composition of claim 34, wherein the aerosol propellant is selected from the group consisting of trichloromonofluoromethane, dichlorotetrafluoroethane, dichlorodifluoromethane, and combinations thereof.

36. The pharmaceutical composition of claim 32, wherein the aerosol propellant is a hydrofluorocarbon.

37. The pharmaceutical composition of claim 36, wherein the aerosol propellant is selected from the group consisting of tetrafluoroethane, heptafluoropropane, and combinations thereof.

38. The pharmaceutical composition of claim 32, wherein the composition comprises a powder having a mean particle size in the range from 0.5 μm to 5 μm.

39. The pharmaceutical composition of claim 32, further comprising a bulking agent.

40. The pharmaceutical composition of claim 39, wherein the bulking agent is selected from the group consisting of sucrose, lactose, trehalose, human serum albumin, glycine, cellobiose, dextrans, maltotriose, pectin, sodium citrate, sodium ascorbate, mannitol, and combinations thereof.

41. The pharmaceutical composition of claim 32, wherein the composition further comprises an additive.

42. The pharmaceutical composition of claim 41, wherein the additive is selected from the group consisting of surfactants, lower alcohols, chemical stabilizers and combinations thereof.

43. The pharmaceutical composition of claim 42, wherein the additive is a surfactant.

44. The pharmaceutical composition of claim 43, wherein the surfactant is selected from the group consisting of oleic acid, sorbitan trioleate, long chain diglycerides, phospholipids, and combinations thereof.

45. The pharmaceutical composition of claim 43, wherein the composition comprises a powder comprised of particles and further wherein the particles are coated with the surfactant.

46. The pharmaceutical composition of claim 41, wherein the additive is a lower alcohol.

47. The pharmaceutical composition of claim 46, wherein the lower alcohol is ethanol.

48. The pharmaceutical composition of claim 41, wherein the additive is a chemical stabilizer.

49. The pharmaceutical composition of claim 48, wherein the chemical stabilizer is selected from the group consisting of buffers, salts, and combinations thereof.

50. The pharmaceutical composition of claim 49, wherein the chemical stabilizer is a buffer.

51. The pharmaceutical composition of claim 50, wherein the buffer is selected from the group consisting of phosphate buffers, citrate buffers, acetate buffers, tris-HCl buffers, and combinations thereof.

52. The pharmaceutical composition of claim 45, wherein the wherein the chemical stabilizer is a salt.

53. The pharmaceutical composition of claim 52, wherein the salt is selected from the group consisting of sodium chloride, sodium carbonate, calcium chloride, and combinations thereof.

54. The pharmaceutical composition of claim 32, wherein the biologically active N-terminal fragment of parathyroid hormone is PTH34.

55. The pharmaceutical composition of claim 32, wherein the biologically active N-terminal fragment of parathyroid hormone is PTH38.

56. A method for treating a mammalian host suffering from or at risk of osteoporosis comprising administering by inhalation through the mouth of the host an aerosolized bolus of a pharmaceutical composition consisting essentially of a therapeutically effective amount of a biologically active N-terminal fragment of parathyroid hormone, a pharmaceutically acceptable bulking agent and an aerosol propellant.

57. The method of claim 56, wherein the mammalian host is human.

58. A method for treating a mammalian host suffering from or at risk of osteoporosis comprising administering by inhalation through the mouth of the host an aerosolized bolus of a pharmaceutical composition comprised of a therapeutically effective amount of a biologically active N-terminal fragment of parathyroid hormone and a propellant, wherein the composition lacks a penetration enhancer.

59. The method of claim 58, wherein the mammalian host is human.